

The question as to how this situation arose is important, and was discussed by a judge at a fatal accident inquiry³ in 2005 into the death of a 5-year-old girl in 2001 from adrenal crisis due to high-dose inhaled fluticasone propionate. It was this death that prompted the recent investigation of adrenal function in children with asthma, prescribed fluticasone propionate >500 µg/day.⁴

At the inquiry, evidence was heard from the treating clinicians and others including a pharmacist, paediatricians, a chest physician, representatives of the Medicines and Healthcare Products Regulatory Agency (formerly the Medicines Control Agency) and GlaxoSmithKline (GSK), the manufacturers of fluticasone propionate. Evidence was heard that at the time of the launch of fluticasone propionate, the product monograph claimed "mean plasma cortisol concentrations remained within the normal range for adults and children, demonstrating that even at high doses (2000 micrograms), fluticasone is well tolerated with regard to systemic effects", and "in a substantial majority of patients, even at daily doses of fluticasone of 2000 micrograms, no adverse effect on adrenal function or reserve has been shown".⁵ In addition GSK promotional literature highlighting safety claims—for example, "negligible oral bioavailability"—was presented. The judge found "that failure by Glaxo to qualify the claims regarding negligible oral bioavailability by referring to the fact that there continued to be absorption of significant amounts of the drug from the lungs, is likely to have made a considerable contribution to a positive view being taken by many members of the medical profession when making decisions about the use of this drug, particularly in high doses".

The Director of Primary Care at GSK had described the dosages used by the prescribing doctors in the case as "exceptional". However, as can be seen in the paper by Paton *et al*, this was clearly not the case, and the judge opined: "it seems to me that, in order to monitor the safety and use of a drug, a drugs company must ensure that it is fully informed as to the way in which the drug is currently being used in clinical practice. Accordingly, consideration of the actual use in practice of fluticasone should have been an essential part of the monitoring of its safety in use." She continued: "the drugs company ought to have taken steps to review a marketing strategy which is based upon safety claims and to remind practitioners of the potential risks of prescribing high doses, even of this drug".

It had also been claimed that the responsibility of "off-licence" prescribing rested with the prescriber; however, the judge commented "it seems to me that a drug manufacturer does not carry out its promotional and marketing functions conscientiously and responsibly if it fails to take this reality (ie, the widespread nature of "off-licence" prescribing in paediatrics) into account. It also seems to me that in the light of this fact, a drugs company must be particularly assiduous in ensuring that extreme caution is exercised when claims are made about the safety of a drug.", and continued: "I am satisfied that the advertising and promotion of fluticasone was aimed at, and contributed towards, establishing a feeling of confidence in the enhanced safety of this particular drug within a medical profession which had already become complacent about the safety of inhaled corticosteroids generally". She concluded: "the emphasis placed upon the

safety of fluticasone in its promotion and marketing, including the advertising of the drug and the fact that no steps were taken by the company, through its representatives or otherwise, to bring to the attention of clinicians at least the changes to the SPC [Summary of Product Characteristics], which were based upon all the evidence available at that time, contributed to the complacency by many within the medical profession about its safety, which in turn contributed to high doses of this drug being prescribed and, accordingly, is a fact that is relevant to the circumstances of this death".

Although the Medicines Control Agency had published a bulletin in 1998⁶ reviewing the safety of inhaled steroids, the judge commented, "the terms of the bulletin were not sufficiently robust and did not sufficiently reflect concern about the practice of prescribing high doses of inhaled corticosteroids, proportionate to the potential risks in so doing".

She also criticised the British Guidelines on Asthma Management 1995 Review and Position Statement,⁷ which "lacked clarity in relation to the maximum recommended dosage of fluticasone for children under 5 years" and that this had contributed to the decision to prescribe high doses of fluticasone in the case.

Finally, she recommended "that the appropriate authorities should consider conducting a review of the practice of general practitioners and hospital specialists when prescribing inhaled corticosteroids, with a view to assessing whether it is appropriate to issue comprehensive guidelines in relation to issues concerning prescribing, specialist referral, informing patients about possible side-effects and monitoring to detect side-effects and in relation to ancillary matters such as the issue of steroid cards". No such review appears imminent and one can only hope that the findings of Paton *et al* provides further evidence for the urgency in carrying out this task.

Paediatricians, GSK and the Medicines and Healthcare products Regulatory Agency (MHRA) were first alerted to the practice of prescribing high-dose fluticasone propionate, and its potential consequences, in 1996.⁸ Unfortunately it has taken the lives of at least 2 children, near deaths of several dozen and a judgement from the fatal accident inquiry to provoke any significant action.

Several questions remain unanswered. Were sufficiently sensitive methods of measuring adrenal suppression used in safety studies? By 1998, GSK had already published data showing that there was no dose response relationship for inhaled fluticasone propionate and 08.00 h cortisol and 24 h urinary cortisol,⁹ so why have many studies continued to use these tests as the main methods for measuring side-effects?¹⁰ Was the MHRA aware of the limitations of these two tests when they increased the licence for fluticasone propionate in children from 200 µg/day to 400 µg/day, and do they still consider them appropriate for assessing the safety of inhaled corticosteroids?

I agree with Russell that the situation with regard to the prescription of high-dose inhaled corticosteroids, which was allowed to develop despite warnings as far back as 1996, was "sphincter-threateningly scary". The prevention of a similar situation arising again will depend on the better control and scrutiny of the pharmaceutical industry's claim for its products, the MHRA better fulfilling its role to protect patients and, most of all, a medical profession independent of drug company

influence and more sceptical about their claims.

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Free vitamin D supplementation for every infant in Turkey

We read with interest the article by Zipitis *et al*¹ concerning primary care trusts providing funds for vitamin D supplementation of Asian children for at least the first 2 years of life.

Nutritional rickets remains prevalent in developing regions of the world such as Africa, the Indian subcontinent, Asia and the Middle East, and ranks among the five most common diseases in children.²⁻⁴ The prevalence of nutritional rickets in developed countries also seems to be rising.⁵⁻¹¹

In Turkey, nutritional rickets has long been among the leading diseases in childhood. Although the prevalence is not known, a recent study indicates that 6% of children <3 years of age presenting to a general outpatient clinic were found to have nutritional rickets.¹² Maternal vitamin D deficiency is also endemic. Severe vitamin D deficiency was identified in 46-80% of pregnant women and nursing mothers in different regions of Turkey.^{13 14} Similarly, almost half of the Turkish adolescent girls have varying degrees of vitamin D deficiency.¹⁵

Several lifestyle and environmental factors are probably responsible for the high prevalence of vitamin D deficiency in developing countries, as well as its resurgence in the developed world. Inadequate exposure to sunlight is becoming more common as individuals spend more time indoors with access to television and computers, or actively avoid the outdoors because of concerns about pollution or the long-term effects of sun exposure on skin cancer. Cultural practices including traditional clothing (covered dress) for women and limited access to open space for pregnant and nursing women also limit adequate sunlight exposure.¹⁶ In addition, there are increasing numbers of women breast feeding and a decrease in the number of doctors routinely prescribing vitamin D supplementation for breastfed infants.^{17, 18} In the face of increasing reports of rickets, the American Academy of Pediatrics, the Department of Health's committee on Medical Aspects of Food Policy in the UK and the European Society of Pediatric Endocrinology developed vitamin D intake guidelines for healthy infants, children and adolescents to prevent vitamin D deficiency and rickets. Daily supplementation of 200–400 IU of vitamin D is recommended to all infants, particularly to those who are exclusively breastfed. However, there are potential problems with the initiation and maintenance of vitamin D supplementation. These include limited public awareness, the cost of supplementation and limited access to healthcare. In 2003, the Bone Health Committee of the Turkish Association of Pediatric Endocrinology issued a consensus document on vitamin D deficiency and its prevention in Turkey. The Turkish Medical Association facilitated its dissemination to all primary care providers. The consensus document defined two specific goals: (1) attain adequate vitamin D status for the whole population, particularly high-risk groups such as infants, children, adolescents, pregnant and nursing women; and (2) ensure early diagnosis and adequate treatment of nutritional rickets and osteomalacia. Proposed public health strategies to achieve these goals were: (1) develop a public awareness campaign to establish adequate sunlight exposure; (2) provide all infants with 400 IU/day of vitamin D supplementation starting at birth; (3) educate primary care providers in the diagnosis and treatment of nutritional rickets and osteomalacia; (4) provide vitamin D supplementation to adolescent girls and women at risk, particularly those using traditional clothing (covered dress); (5) advocate for regulation mandating vitamin D enrichment of all dairy products. In 2004, the committee appealed to the Ministry of Health of Turkey to assume a leadership role in realising these strategies. In May 2005, the Ministry of Health initiated a 5-year project coordinated by the General Directorate of Maternal Child Health and Family Planning. This project will implement all the proposed strategies. A nationwide campaign has been launched to encourage the entire population, particularly pregnant and nursing women and infants, to have adequate sunlight exposure. A curriculum has been developed to train health-care workers. The most significant step, however, is that the Ministry of Health will distribute vitamin D supplements to every newborn throughout infancy at no financial cost to families through its network of primary care units and maternal-child health centres. This should undoubtedly improve access to

vitamin D supplementation and compliance with its use. We believe this initiative is a major step towards eliminating nutritional rickets in Turkey. It also is a unique opportunity to establish a model for populations in which vitamin D deficiency is a significant child health problem.

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Postnatal weight monitoring should be routine

The case reports of Shroff *et al*¹ document a serious clinical problem with potentially devastating consequences. The tragedy of this situa-

tion is that the affected infants are all perfectly healthy and, if we only look for it, the condition is preventable. Local experience of precisely such a case led to the introduction of routine postnatal weight monitoring of infants during the first 2 weeks of life. This policy met with a great deal of resistance on the basis of three unsubstantiated arguments: that inadequately feeding infants can be recognised from other clinical cues, that we don't know what degree of weight loss is acceptable, and that demonstrating weight loss will discourage mothers from continuing to breast feed.

Hypernatraemic dehydration associated with breast feeding is a problem in the UK.^{2–4} Our experience⁵ and that of Shroff *et al* denies that inadequately feeding infants can be reliably recognised from other clinical cues. Infants who are not adequately breast fed have been reviewed by doctors, health visitors and midwives, without any recognition of the clinical problem. If the problem is not recognised, owing to subjective clinical assessment, then it cannot be remedied. In contrast, monitoring postnatal weight loss provides an objective assessment of the adequacy of nutritional intake, allowing targeted support to the mothers of those infants who are failing to thrive or are showing excessive weight loss.

Claims that we don't know what degree of weight loss is acceptable have been addressed by our study of postnatal weight change, which set out clear upper centiles for the degree and timing of initial weight loss and time taken to regain birth weight.⁶ This has allowed us to develop clear guidelines for providing additional support to breastfeeding mothers. We now weigh babies routinely around days 3, 6 and 10 with continued monitoring of those who have not regained their birth weight. Breastfed infants with >10% weight loss are referred to specialist breastfeeding-support sisters for supervised feeding, advice on positioning and milk expression. In addition, paediatric medical staff see and monitor infants who lose >12.5% of their birth weight.

Anecdotal cases may suggest that demonstrating weight loss or poor gain could discourage mothers from continuing to breast feed; however, other mothers may be reassured and encouraged to continue breast feeding. We have found no evidence that such weight monitoring discourages mothers from continuing to breast feed.⁷ Our monitored population (in contrast to two local control groups) actually showed an increase in 6-week breastfeeding rates after introducing a policy of routine weight monitoring.

It would be nice if that which was natural and best could always be easily established, but we must recognise that sometimes it can be hard. We will serve breastfeeding mothers best if we identify those who are having difficulties and provide early help and support. The arguments against routine weight monitoring have been addressed, and it is time to offer this safety net to all infants.

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